

REMARKS

Claims 1-32 are pending in the present application.

The rejection of Claims 1-23¹ under 35 U.S.C. §112, first paragraph (enablement), is obviated in part by amendment and traversed in part.

At the outset, Applicants thank Examiner Roberts for the recognition that the present application enables a method for “ameliorating, progress blocking and therapeutically treating one or more stress induced diseases.” (see page 2, lines 20-22 of Office Action mailed August 24, 2007). With respect to the Examiner’s alleged lack of enablement for claims drawn to “preventing one or more stress induced diseases” (Claims 33-56 in the elected invention), Applicants make no statement with respect to the propriety of these allegations and in no way acquiesce to the same. Nonetheless, to expedite examination of the claims that the Examiner recognizes as being enabled, Applicants have canceled Claims 33-56 herein. Therefore, this ground of rejection is believed to be moot.

Applicants request withdrawal of these grounds of rejection.

The rejections of: (a) Claims 1-11, 13, 15-20, and 22-23 under 35 U.S.C. §102(b) over Schaefer et al, and (b) Claim 12 under 35 U.S.C. §103(a) over Schaefer et al, are respectfully traversed.

Schaefer et al disclose a method of treating antemortem stress for livestock. The Examiner takes the position that “panic disorders and general anxiety disorders” embrace panic due to antemortem stress. The Examiner’s alleges that “panic disorders and general anxiety disorders” are not defined in the specification, because “Applicant does not appear to

¹ Note: the Examiner improperly lists Claims 1-23 as being rejected. These claims do not recite “preventing”. The claims reciting this limitation are Claims 33-56.

give specific examples of what is encompassed by the disorders as they apply to animals such as cattle". Thus, the Examiner alleges that antemortem stress falls within the scope of either "panic disorders" and "general anxiety disorders" because antemortem stress is actually panic "because the animal is about to be slaughtered and therefore... antemortem stress is due to panic because the animal is aware it is in danger and therefore panics". The Examiner further alleges that even if it were proven that antemortem stress is not a panic disorder or a general anxiety disorder, it would qualify as an emotion disorder. The basis for this allegation is, again, that "emotion disorder" is not defined in the specification.

Applicants respectfully disagree with the Examiner's allegations and characterization of antemortem stress as being within the scope of either "panic disorders" and "general anxiety disorders". Applicants submit that "emotion disorder", "panic disorder", and "general anxiety disorder" are not recognized terms and that the recognized definition for these terms would exclude "antemortem stress". To evidence the same, Applicants **submit herewith** KAPLAN & SADOCK'S, *Synopsis Of Psychiatry Tenth Edition*, (2007) Lippincott Williams & Wilkins. According to DSM-IV TR, diagnostic criteria for generalized anxiety disorder is shown in Table 16.6-2 on page 624. The essential characteristics of "general anxiety disorder" are sustained and excessive anxiety and worry accompanied by a number of physiological symptoms. According to ICD-10, there must have been a period of at least 6 months with prominent tension, worry, and feeling of apprehension about every day events and problems (see Table 16.1-4 on page 585). In the diagnostic criteria for "panic disorder" of ICD-10, the panic attacks are not associated with marked exertion or with exposure to dangerous or life-threatening situations. The "emotion disorder" is also included in such a human psychiatric disorder.

Schaefer et al define the term “antemortem stress” at column 3, lines 13-19 as:

The terms "antemortem period" and "antemortem stress", when used herein and in the claims, refer to the time and stresses imparted to animals during pre-slaughter treatment, including transport, holding, management, and handling. The terms are also meant to include stresses imparted during other animal marketing practices, such as transporting animals for other than slaughter purposes.

Clearly, the term “antemortem stress” as used in Schaefer et al is clinically distinct from “emotion disorder”, “panic disorder”, and “general anxiety disorder”. Therefore, Schaefer et al does not anticipate the claimed invention.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 1-17, 20-23, 27, 30-47, and 52-56 under 35 U.S.C. §103(a) over Chen et al in view of Pitman is respectfully traversed.

The Examiner cites paragraph [0073] of Pitman for the administration of a combination of lycopene and lysine to certain subjects. However, in paragraph [0073] of Pitman subject #3 is described as having symptoms of memory loss and anxiety. Anxiety in Pitman does not qualify in the clinically recognized classes of individuals referred to by the term “anxiety disorders” in the present application. More specifically, as recognized by the Examiner, Pitman does not disclose or suggest anxiety disorders panic disorder or general anxiety disorder.

Recognizing this deficiency, the Examiner cites Chen et al and alleges that this reference discloses “anxiety disorders” at column 19, lines 35-61.² However, contrary to the allegation by the Examiner, Chen et al does not specifically disclose or suggest administering a composition containing lysine to treat anxiety disorders. The disclosure at column 19, lines 35-61 relates to the administration of compositions comprising β-interferon or variants

² Apparently, improperly listed as column 19, lines 14-34.

thereof. No specific motivation is given to administer lysine together with β -interferon, much less for the treatment of anxiety disorders. Accordingly, Applicants submit that the combined disclosures of Chen et al and Pitman do not render the present invention obvious since, based on these references, the artisan would have been given no reason to administer the claimed composition for ameliorating, progress blocking, or therapeutically treating one or more stress-induced diseases specified in the claimed invention.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter, Ph.D.
Registration No. 32,884

Customer Number

22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)

Vincent K. Shier, Ph.D.
Registration No. 50,552

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VIRGINIA A. SADOCK, MD

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Table 16.1-3
ICD-10 Diagnostic Criteria for Phobic Anxiety Disorders

Agoraphobia	Social phobias
A. There is marked and consistently manifest fear in, or avoidance of, at least two of the following situations:	A. Either of the following must be present.
(1) crowds; (2) public places; (3) traveling alone; (4) traveling away from home.	(1) marked fear of being the focus of attention, or fear of behaving in a way that will be embarrassing or humiliating; (2) marked avoidance of being the focus of attention, or of situations in which there is fear of behaving in an embarrassing or humiliating way.
B. At least two symptoms of anxiety in the feared situation must have been present together, on at least one occasion since the onset of the disorder, and one of the symptoms must have been from items (1) to (4) listed below.	These fears are manifested in social situations, such as eating or speaking in public, encountering known individuals in public or entering or enduring small group situations (e.g., parties, meetings, classrooms).
Autonomic arousal symptoms	B. At least two symptoms of anxiety in the feared situation as defined in agoraphobia, Criterion B, must have been manifest at some time since the onset of the disorder, together with at least one of the following symptoms:
(1) palpitations or pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) dry mouth (not due to medication or dehydration);	(1) blushing or shaking; (2) fear of vomiting; (3) urgency or fear of micturition or defecation.
Symptoms Involving chest and abdomen	C. Significant emotional distress is caused by the symptoms or by the avoidance, and the individual recognizes that these are excessive or unreasonable.
(5) difficulty in breathing; (6) feeling of choking; (7) chest pain or discomfort; (8) nausea or abdominal distress (e.g., churning in stomach);	D. Symptoms are restricted to, or predominate in, the feared situations or contemplation of the feared situations.
Symptoms involving mental state	E. <i>Most commonly used exclusion clause.</i> The symptoms listed in Criteria A and B are not the result of delusions, hallucinations, or other disorders such as organic mental disorders, schizophrenia and related disorders, mood [affective] disorders, or obsessive-compulsive disorder, and are not secondary to cultural beliefs.
(9) feeling dizzy, unsteady, faint, or light-headed; (10) feelings that objects are unreal (derealization), or that the self is distant or "not really here" (depersonalization); (11) fear of losing control, "going crazy," or passing out; (12) fear of dying	Specific (isolated) phobias.
General symptoms	A. Either of the following must be present:
(13) hot flushes or cold chills; (14) numbness or tingling sensations.	(1) marked fear of a specific object or situation not included in agoraphobia or social phobia; (2) marked avoidance of a specific object or situation not included in agoraphobia or social phobia.
C. Significant emotional distress is caused by the avoidance or by the anxiety symptoms, and the individual recognizes that these are excessive or unreasonable.	Among the most common objects and situations are animals, birds, insects, heights, thunder, flying, small enclosed spaces the sight of blood or injury, injections, dentists, and hospitals.
D. Symptoms are restricted to, or predominate in, the feared situations or contemplation of the feared situations.	B. Symptoms of anxiety in the feared situation as defined in agoraphobia, Criterion B, must have been manifest at some time since the onset of the disorder.
E. <i>Most commonly used exclusion clause.</i> Fear or avoidance of situations (Criterion A) is not the result of delusions, hallucinations, or other disorders such as organic mental disorders, schizophrenia and related disorders, mood [affective] disorders, or obsessive-compulsive disorder, and is not secondary to cultural beliefs.	C. Significant emotional distress is caused by the symptoms or by the avoidance, and the individual recognizes that these are excessive or unreasonable.
The presence or absence of panic disorder in a majority of agoraphobic situations may be specified by using a fifth character.	D. Symptoms are restricted to the feared situation or contemplation of the feared situation. If desired, the specific phobias may be subdivided as follows.
Without panic disorder	—animal type (e.g., insects, dogs) —nature-forces type (e.g., storms, water) —blood, injection, and injury type. —situation type (e.g., elevators, tunnels) —other type
With panic disorder	
Options for rating severity	
Severity in agoraphobia may be rated by indicating the degree of avoidance, taking into account the specific cultural setting. Severity in social phobias may be rated by counting the number of panic attacks.	Other phobic anxiety disorders Phobic anxiety disorder, unspecified

(From World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. Copyright, World Health Organization, Geneva, 1993, with permission.)

Table 16.1-4
ICD-10 Diagnostic Criteria for Other Anxiety Disorders

Panic disorder [episodic paroxysmal anxiety]

- A. The individual experiences recurrent panic attacks that are not consistently associated with a specific situation or object and that often occur spontaneously (i.e., the episodes are unpredictable). The panic attacks are not associated with marked exertion or with exposure to dangerous or life-threatening situations.
- B. A panic attack is characterized by all of the following:
- (1) it is a discrete episode of intense fear of discomfort;
 - (2) it starts abruptly;
 - (3) it reaches a maximum within a few minutes and lasts at least some minutes;
 - (4) at least four of the symptoms listed below must be present, one of which must be from items (a) to (d):
- Autonomic arousal symptoms**
- (a) palpitations or pounding heart, or accelerated heart rate;
 - (b) sweating;
 - (c) trembling or shaking;
 - (d) dry mouth (not due to medication or dehydration);
- Symptoms involving chest and abdomen**
- (e) difficulty in breathing;
 - (f) feeling of choking;
 - (g) chest pain or discomfort;
 - (h) nausea or abdominal distress (e.g., churning in stomach);
- Symptoms Involving mental state**
- (i) feeling dizzy, unsteady, faint, or light-headed;
 - (j) feeling that objects are unreal (derealization), or that the self is distant or "not really here" (depersonalization);
 - (k) fear of losing control, "going crazy," or passing out;
 - (l) fear of dying;
- General symptoms**
- (m) hot flushes or cold chills;
 - (n) numbness or tingling sensations.

C. **Most commonly used exclusion clause.** Panic attacks are not due to a physical disorder, organic mental disorder, or other mental disorders, such as schizophrenia and related disorders, mood [affective] disorders, or somatoform disorders.

The range of individual variation in both content and severity is so great that two grades, moderate and severe, may be specified, if desired, with a fifth character.

Panic disorder, moderate

At least four panic attacks in a 4-week period.

Panic disorder, severe

At least four panic attacks per week over a 4-week period.

Generalized anxiety disorder.

Note. In children and adolescents the range of complaints by which the general anxiety is manifest is often more limited than in adults, and the specific symptoms of autonomic arousal are often less prominent. For these individuals, an alternative set of criteria is provided for use (in generalized anxiety disorder of childhood) if preferred.

- A. There must have been a period of at least 6 months with prominent tension, worry, and feelings of apprehension about everyday events and problems.

- B. At least four of the symptoms listed below must be present, at least one of which must be from items (1) to (4):

Autonomic arousal symptoms

- (1) palpitations or pounding heart, or accelerated heart rate;
- (2) sweating;
- (3) trembling or shaking;
- (4) dry mouth (not due to medication or dehydration);

Symptoms involving chest and abdomen

- (5) difficulty in breathing;
- (6) feeling of choking;
- (7) chest pain or discomfort;
- (8) nausea or abdominal distress (e.g., churning in stomach);

Symptoms involving mental state

- (9) feeling dizzy, unsteady, faint, or light-headed;
- (10) feelings that objects are unreal (derealization), or that the self is distant or "not really here" (depersonalization);
- (11) fear of losing control, "going crazy," or passing out;
- (12) fear of dying;

General symptoms

- (13) hot flushes or cold chills;
- (14) numbness or tingling sensations;

Symptoms of tension

- (15) muscle tension or aches and pains;
- (16) restlessness and inability to relax;
- (17) feeling keyed up, on edge, or mentally tense;
- (18) a sensation of a lump in the throat, or difficulty in swallowing;

Other nonspecific symptoms

- (19) exaggerated response to minor surprise or being startled;
- (20) difficulty in concentrating, or mind "going blank," because of worrying or anxiety;
- (21) persistent irritability;
- (22) difficulty in getting to sleep because of worrying.

- C. The disorder does not meet the criteria for panic disorder, phobic anxiety disorders, obsessive-compulsive disorder, or hypochondriacal disorder.

- D. **Most commonly used exclusion clause.** The anxiety disorder is not due to a physical disorder, such as hyperthyroidism, an organic mental disorder, or a psychoactive substance-related disorder, such as excess consumption of amphetaminelike substances or withdrawal from benzodiazepines.

Mixed anxiety and depressive disorder

There are so many possible combinations of comparatively mild symptoms for these disorders that specific criteria are not given other than those already in *Clinical Descriptions and Diagnostic Guidelines*. It is suggested that researchers wishing to study patients with these disorders should arrive at their own criteria within the guidelines, depending upon the setting and purpose of their studies.

Other mixed anxiety disorders**Other specified anxiety disorders****Anxiety disorder, unspecified**

abnormal findings in the right hemisphere but not the left hemisphere; this finding suggests that some types of cerebral asymmetries may be important in the development of anxiety disorder symptoms in specific patients. Functional brain-imaging (fMRI) studies—for example, positron emission tomography (PET), single photon emission computed tomography (SPECT), and electroencephalography (EEG)—of patients with anxiety disorder have variously reported abnormalities in the frontal cortex, the occipital and temporal areas, and, in a study of panic disorder, the parahippocampal gyrus. Several functional neuroimaging studies have implicated the caudate nucleus in the pathophysiology of OCD. In posttraumatic stress disorder, fMRI studies have found increased activity in the amygdala, a brain region associated with fear (see Color Plate Fig. 16.1–1 on p. 494). A conservative interpretation of these data is that some patients with anxiety disorders have a demonstrable functional cerebral pathological condition and that the condition may be causally relevant to their anxiety disorder symptoms.

Genetic Studies. Genetic studies have produced solid evidence that at least some genetic component contributes to the development of anxiety disorders. Heredity has been recognized as a predisposing factor in the development of anxiety disorders. Almost half of all patients with panic disorder have at least one affected relative. The figures for other anxiety disorders, although not as high, also indicate a higher frequency of the illness in first-degree relatives of affected patients than in the relatives of nonaffected persons. Although adoption studies with anxiety disorders have not been reported, data from twin registers also support the hypothesis that anxiety disorders are at least partially genetically determined. Clearly, a linkage exists between genetics and anxiety disorders, but no anxiety disorder is likely to result from a simple mendelian abnormality. One report has attributed about 4 percent of the intrinsic variability of anxiety within the general population to a polymorphic variant of the gene for the serotonin transporter, which is the site of action of many serotonergic drugs. Persons with the variant produce less transporter and have higher levels of anxiety.

In 2005, a scientific team, led by National Institute of Mental Health (NIMH) grantee and Noble Laureate Dr. Eric Kandel demonstrated that knocking out a gene in the brain's fear hub creates mice unperturbed by situations that would normally trigger instinctive or learned fear responses. The gene codes for *stathmin*, a protein that is critical for the amygdala to form fear memories. Stathmin knockout mice showed less anxiety when they heard a tone that had previously been associated with a shock, indicating less learned fear. The knockout mice also were more susceptible to explore novel open space and maze environments, a reflection of less innate fear. Kandel suggests that stathmin knockout mice can be used as a model of anxiety states of mental disorders with innate and learned fear components: these animals could be used to develop new antianxiety agents. Whether stathmin is similarly expressed and pivotal for anxiety in the human amygdala remains to be confirmed.

Neuroanatomical Considerations. The locus ceruleus and the raphe nuclei project primarily to the limbic system and the cerebral cortex. In combination with the data from brain-imaging studies, these areas have become the focus of much hypothesis-forming about the neuroanatomical substrates of anxiety disorders.

LIMBIC SYSTEM. In addition to receiving noradrenergic and serotonergic innervation, the limbic system also contains a high concentration of GABA_A receptors. Ablation and stimulation studies in nonhuman primates have also implicated the limbic system in the generation of anxiety and fear responses. Two areas of the limbic system have received special attention in the literature: increased activity in the septohippocampal pathway, which may lead to anxiety, and the cingulate gyrus, which has been implicated particularly in the pathophysiology of OCD.

CEREBRAL CORTEX. The frontal cerebral cortex is connected with the parahippocampal region, the cingulate gyrus, and the hypothalamus and, thus, may be involved in the production of anxiety disorders. The temporal cortex has also been implicated as a pathophysiological site in anxiety disorders. This association is based in part on the similarity in clinical presentation and electrophysiology between some patients with temporal lobe epilepsy and patients with OCD.

16.1.1

In the 10th revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10), neurotic (anxiety) disorders are grouped with stress-related and somatoform disorders because of "their historical association with the concept of neurosis and the association of a substantial (although uncertain) proportion of these disorders with psychological causation." In ICD-10, mixtures of symptoms are described

**Table 16.1-5
ICD-10 Diagnostic Criteria for
Obsessive-Compulsive Disorder**

- A. Either obsessions or compulsions (or both) are present on most days for a period of at least 2 weeks.
- B. Obsessions (thoughts, ideas, or images) and compulsions (acts) share the following features, all of which must be present:
 - (1) They are acknowledged as originating in the mind of the patient and are not imposed by outside persons or influences.
 - (2) They are repetitive and unpleasant, and at least one obsession or compulsion that is acknowledged as excessive or unreasonable must be present.
 - (3) The patient tries to resist them (but resistance to very long-standing obsessions or compulsions may be minimal). At least one obsession or compulsion that is unsuccessfully resisted must be present.
 - (4) Experiencing the obsessive thought or carrying out the compulsive act is not in itself pleasurable. (This should be distinguished from the temporary relief of tension or anxiety.)
- C. The obsessions or compulsions cause distress or interfere with the patient's social or individual functioning, usually by wasting time.
- D. *Most commonly used exclusion clause.* The obsessions or compulsions are not the result of other mental disorders, such as schizophrenia and related disorders or mood [affective] disorders.

The diagnosis may be further specified by the following four-character codes:

- Predominantly obsessional thoughts and ruminations
- Predominantly compulsive acts [obsessional rituals]
- Mixed obsessional thoughts and acts
- Other obsessive-compulsive disorders
- Obsessive-compulsive disorder, unspecified

Table 16.1-6
ICD-10 Diagnostic Criteria for Reactions to Severe Stress

Acute stress reaction

- A. The patient must have been exposed to an exceptional mental or physical stressor.
- B. Exposure to the stressor is followed by an immediate onset of symptoms (within 1 hour).
- C. Two groups of symptoms are given: the acute stress reaction is graded as:
 - Mild
Only Criterion (1) below is fulfilled.
 - Moderate
Criterion (1) is met, and there are any two symptoms from Criterion (2).
 - Severe
Either criterion (1) is met, and there are any four symptoms from criterion (2); or there is dissociative stupor.
- (1) Criteria B, C, and D for generalized anxiety disorder are met.
- (2) (a) Withdrawal from expected social interaction.
 (b) Narrowing of attention
 (c) Apparent disorientation
 (d) Anger or verbal aggression
 (e) Despair or hopelessness
 (f) Inappropriate or purposeless overactivity
 (g) Uncontrollable and excessive grief (judged by local cultural standards).
- D. If the stressor is transient or can be relieved, the symptoms must begin to diminish after not more than 8 hours. If exposure to the stressor continues, the symptoms must begin to diminish after not more than 48 hours.
- E. **Most commonly used exclusion clause.** The reaction must occur in the absence of any other concurrent mental or behavioral disorder in ICD-10 (except generalized anxiety disorder and personality disorders) and not within 3 months of the end of an episode of any other mental or behavioral disorder.

Posttraumatic stress disorder

- A. The patient must have been exposed to a stressful event or situation (either short- or long-lasting) of an exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone.
- B. There must be persistent remembering or "reliving" of the stressor in intrusive "flashbacks," vivid memories, or recurring dreams or in experiencing distress when exposed to circumstances resembling or associated with the stressor.
- C. The patient must exhibit an actual or preferred avoidance of circumstances resembling or associated with the stressor, which was not present before exposure to the stressor.
- D. Either of the following must be present:
 - (1) inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor;
 - (2) persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor), shown by any two of the following:
 - (a) difficulty in falling or staying asleep;
 - (b) irritability or outbursts of anger;
 - (c) difficulty in concentrating;
 - (d) hypervigilance;
 - (e) exaggerated startle response.
- E. Criteria B, C, and D must all be met within 6 months of the stressful event or of the end of a period of stress. (For some purposes, onset delayed more than 6 months may be included, but this should be clearly specified.)

(From World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. Copyright, World Health Organization, Geneva, 1993, with permission.)

as common, especially in less-severe varieties of these disorders, and a category for cases that cannot be based on a single main syndrome is provided. Although the idea of neurosis is no longer the organizing principle, "care has been taken to allow the easy identification of disorders that some users still might wish to regard as neurotic in their own usage of the term."

The main ICD-10 categories for "neurotic" anxiety disorders are phobic anxiety disorders (agoraphobia, social phobias, and specific phobias); other anxiety disorders (panic disorder, generalized anxiety disorder, and mixed anxiety and depressive disorder); and OCD (with predominantly obsessional thoughts, predominantly compulsive acts, or mixed obsessional thoughts and acts) (Tables 16.1-3 through 16.1-5).

In ICD-10, reaction to severe stress and adjustment disorders are grouped into one category, which is classed together with neurotic and somatoform disorders. The stress-related category differs from the other two categories, however, because it can be defined on the basis of both symptoms and one of two causative influences: a stressful life event causing an acute stress reaction or a significant life change producing an adjustment disorder. Stress-related disorders in all age groups, including children, fall into this category.

In this group, ICD-10 classifies reactions to severe stress (acute stress reaction, posttraumatic distress disorder) and adjustment disorders (see Chapter 26). ICD-10 also includes the dissociative (conversion) disorders in the category of stress-related disorders. (For a discussion of dissociative disorders, see Chapter 20.) The criteria for reactions to severe stress are given in Table 16.1-6.

REFERENCES

- Charney DS. Anxiety disorders: Introduction and overview. In: Sadock BJ, Sadock VA, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 8th ed. Vol. 1. Baltimore: Lippincott Williams & Wilkins; 2005:1718.
- Doyle AC, Pollack MH. Establishment of remission criteria for anxiety disorders. *J Clin Psychiatry*. 2003;64[Suppl 15]:40-45.
- Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. *Arch Gen Psychiatry*. 2005;62:182-189.
- Pigott TA. Anxiety disorders in women. *Psychiatr Clin North Am*. 2003;26: 621-672.
- Schulz J, Gatto JG, Rapaport MH. The diagnosis and treatment of generalized anxiety disorder. *Primary Psychiatry*. 2005;12:58-67.
- Schwartz CE, Wright CI, Shin LM, Kagan J, Rauch SL. Inhibited and uninhibited infants "grown up": Adult amygdala response to novelty. *Science*. 2003;300:1052-1053.
- Stein MB. Attending to anxiety disorders in primary care. *J Clin Psychiatry*. 2003;64[Suppl 15]:35-39.
- Sussman N. Anxiety disorders in the clinical setting. *Primary Psychiatry*. 2005;12:12.
- Velting ON, Szczer NJ, Albano AM. Update on and advances in assessment and cognitive-behavioral treatment of anxiety disorders in children and adolescents. *Professional Psychology—Research & Practice*. 2004;35:42-54.
- Wittchen HU, Beesdo K, Bittner A, Goodwin RD. Depressive episodes: Evidence for a causal role of primary anxiety disorders? *Eur Psychiatry*. 2003;18:384-393.

▲ 16.2 Panic Disorder and Agoraphobia

An acute intense attack of anxiety accompanied by feelings of impending doom is known as *panic disorder*. The anxiety is characterized by discrete periods of intense fear that can vary from several attacks during one day to only a few attacks during a year. Patients with panic disorder present with a number of comorbid conditions, most commonly agoraphobia, which refers to a fear of or anxiety regarding places from which escape might be difficult.

- comorbid with major depression: Factors mediating the association with suicidal behavior. *Am J Psychiatry*. 2005;162:560-566.
- Palyo SA, Beck JG. Post-traumatic stress disorder symptoms, pain, and perceived life control: Associations with psychosocial and physical functioning. *Pain*. 2005;117:121-127.
- Wilson JP, Drozdek B, Turkovic S. Posttraumatic Shame and Guilt. *Trauma, Violence & Abuse*. 2006;7:122-141.

▲ 16.6 Generalized Anxiety Disorder

Anxiety can be conceptualized as a normal and adaptive response to threat that prepares the organism for flight or fight. Persons who seem to be anxious about almost everything, however, are likely to be classified as having generalized anxiety disorder. The text revision of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) defines generalized anxiety disorder as excessive anxiety and worry about several events or activities for most days during at least a 6-month period. The worry is difficult to control and is associated with somatic symptoms, such as muscle tension, irritability, difficulty sleeping, and restlessness. The anxiety is not focused on features of another Axis I disorder, is not caused by substance use or a general medical condition, and does not occur only during a mood or psychiatric disorder. The anxiety is difficult to control, is subjectively distressing, and produces impairment in important areas of a person's life.

EPIDEMIOLOGY

Generalized anxiety disorder is a common condition; reasonable estimates for its 1-year prevalence range from 3 to 8 percent. The ratio of women to men with the disorder is about 2 to 1, but the ratio of women to men who are receiving inpatient treatment for the disorder is about 1 to 1. A lifetime prevalence is close to 5 percent with the Epidemiological Catchment Area (ECA) study suggesting a lifetime prevalence as high as 8 percent. In anxiety disorder clinics about 25 percent of patients have generalized anxiety disorder. The disorder usually has its onset in late adolescence or early adulthood, although cases are commonly seen in older adults. Also, some evidence suggests that the prevalence of generalized anxiety disorder is particularly high in primary care settings.

COMORBIDITY

Generalized anxiety disorder is probably the disorder that most often coexists with another mental disorder, usually social phobia, specific phobia, panic disorder, or a depressive disorder. Perhaps 50 to 90 percent of patients with generalized anxiety disorder have another mental disorder. As many as 25 percent of patients eventually experience panic disorder. Generalized anxiety disorder is differentiated from panic disorder by the absence of spontaneous panic attacks. An additional high percentage of patients are likely to have major depressive disorder. Other common

disorders associated with generalized anxiety disorder are dysthymic disorder and substance-related disorders.

ETIOLOGY

The cause of generalized anxiety disorder is not known. As currently defined, generalized anxiety disorder probably affects a heterogeneous group of persons. Perhaps because a certain degree of anxiety is normal and adaptive, differentiating normal anxiety from pathological anxiety and differentiating biological causative factors from psychosocial factors are difficult. Biological and psychological factors probably work together.

Biological Factors

The therapeutic efficacies of benzodiazepines and the azaspirones (e.g., buspirone [BuSpar]) have focused biological research efforts on the γ -aminobutyric acid and serotonin neurotransmitter systems. Benzodiazepines (which are benzodiazepine receptor agonists) are known to reduce anxiety, whereas flumazenil (Romazicon) (a benzodiazepine receptor antagonist) and the β -carbolines (benzodiazepine receptor reverse agonists) are known to induce anxiety. Although no convincing data indicate that the benzodiazepine receptors are abnormal in patients with generalized anxiety disorder, some researchers have focused on the occipital lobe, which has the highest concentrations of benzodiazepine receptors in the brain. Other brain areas hypothesized to be involved in generalized anxiety disorder are the basal ganglia, the limbic system, and the frontal cortex. Because buspirone is an agonist at the serotonin 5-HT_{1A} receptor, there is the hypothesis that the regulation of the serotonergic system in generalized anxiety disorder is abnormal. Other neurotransmitter systems that have been the subject of research in generalized anxiety disorder include the norepinephrine, glutamate, and cholecystokinin systems. Some evidence indicates that patients with generalized anxiety disorder may have subsensitivity of their α_2 -adrenergic receptors, as indicated by a blunted release of growth hormone after clonidine (Catapres) infusion.

Brain-imaging studies of patients with generalized anxiety disorder have revealed significant findings. One positron emission tomography study reported a lower metabolic rate in basal ganglia and white matter in patients with generalized anxiety disorder than in normal control subjects (Fig. 16.6-1). A few genetic studies have also been conducted in the field. One study found that a genetic relation might exist between generalized anxiety disorder and major depressive disorder in women. Another study showed a distinct, but difficult-to-quantitate, genetic component in generalized anxiety disorder. About 25 percent of first-degree relatives of patients with generalized anxiety disorder are also affected. Male relatives are likely to have an alcohol use disorder. Some twin studies report a concordance rate of 50 percent in monozygotic twins and 15 percent in dizygotic twins. Table 16.6-1 lists relative genetic risks in selected anxiety disorders.

A variety of electroencephalogram (EEG) abnormalities has been noted in alpha rhythm and evoked potentials. Sleep EEG studies have reported increased sleep discontinuity, decreased delta sleep, decreased stage 1 sleep, and reduced rapid eye movement sleep. These changes in sleep architecture differ from the changes seen in depressive disorders.

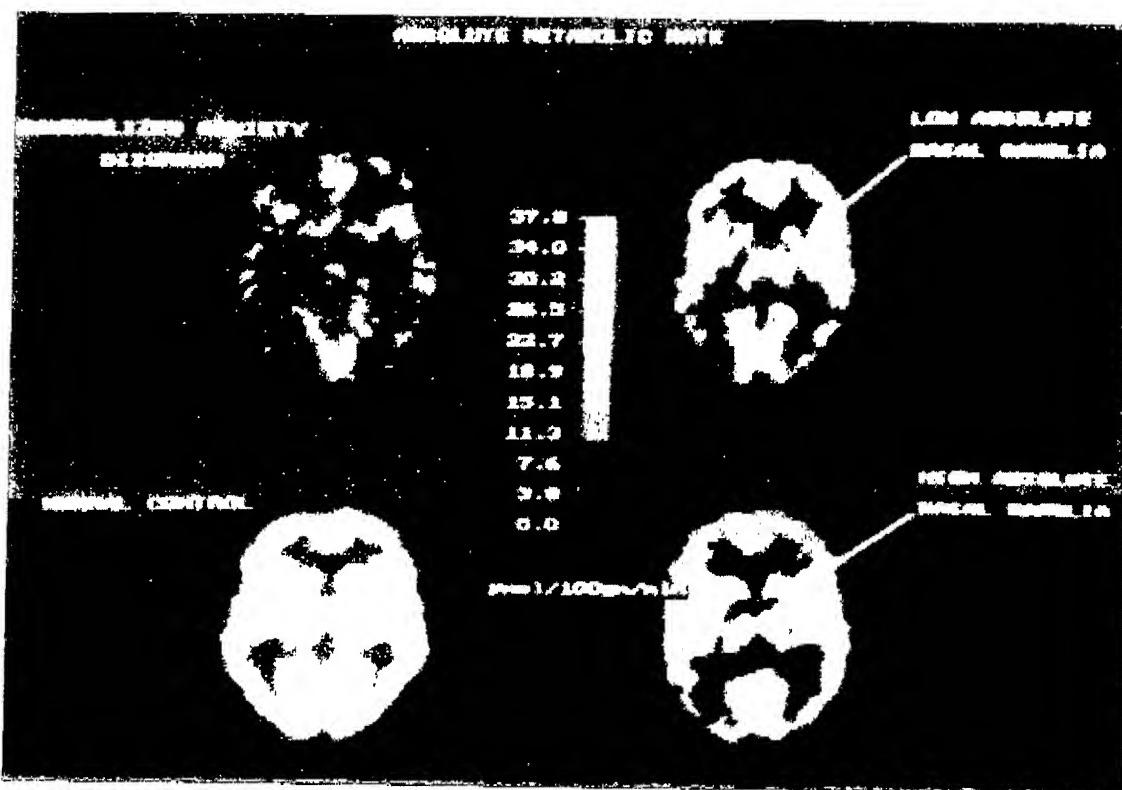


FIGURE 16.6-1

Basal ganglia metabolism. A common glucose scale shows the decrease in absolute glucose metabolic rate in the basal ganglia of two typical subjects with generalized anxiety disorder (top row) compared with two normal control subjects (bottom row). (From Wu JC, Buchsbaum MS, Hershey TG, Hazlett E, Sicotte N, Johnson JC. PET in generalized anxiety disorder. *Biol Psychiatry* 1991;29:1188, with permission.)

Psychosocial Factors

The two major schools of thought about psychosocial factors leading to the development of generalized anxiety disorder are the cognitive-behavioral school and the psychoanalytic school. According to the cognitive-behavioral school, patients with generalized anxiety disorder respond to incorrectly and inaccurately perceived dangers. The inaccuracy is generated by selective attention to negative details in the environment, by distortions in information processing, and by an overly negative view of the person's own ability to cope. The psychoanalytic school hypothesizes that anxiety is a symptom of unresolved, unconscious conflicts. Sigmund Freud first presented this psychological theory in 1909 with his description of Little Hans; before then, Freud had conceptualized anxiety as having a physiological basis. An

example of Freudian theory as applied to general anxiety can be seen in the following case:

Mrs. B, a 26-year-old married woman, was admitted to the hospital for the evaluation of persistent anxiety that had begun 8 months earlier and was becoming increasingly disabling. Especially disturbing to the patient was the spontaneous intrusion of intermittent images in her mind's eye of her father and herself locked in a naked sexual embrace. The images were not only frightening, but they puzzled her greatly, for she had always disliked her father intensely. Not only was he "poison" to her, but she tried to avoid any contact with him and found it difficult to talk to him if she was forced to be in his company.

As the patient described the difficulty of her relationship with her father, she suddenly recalled that her anxiety had begun at a time when her father was seemingly being more intrusive than ever as he tried to help her and her husband over a period of financial difficulty.

As the patient continued to revile her father, she suddenly commented that her mother had told her that her father "had been good to me when I was little and he used to sing songs to me and take me on his lap, but I don't remember. I only remember when he was mean to me. I just am glad when he keeps on talking mean to me the way he always has. I just wouldn't know what to do if he was nice to me." When asked by the interviewer if there might have been a time when she had wanted him to be nice to her, the patient replied, "When I was little, I just wanted to know that he did love me a little. I guess I always wanted him to be nice to me. But when I stop to think about it, I guess I didn't want him to be nice to me." The doctor then



Table 16.6-1
Familial Relative Risks in Selected Anxiety Disorders

Disorder	Population Prevalence (%)	Familial Relative Risk ^a
Panic disorder	1-3	2-20
Generalized anxiety disorder	3-5	6
Obsessive-compulsive disorder	1-3	3-5

^aRatio of risk to relatives of cases versus risk to relatives of controls

commented, "It sounds as if a part of you wants to be close to your father." In response, the patient burst into agitated sobs and blurted out, "I don't know how to be close to my father! I am too old to care about my father now!"

When the patient regained her composure, she recalled the memory of an event she had not thought of since it had occurred 15 years earlier. When she was 11, she reported, while in the living room with her father, she had suddenly had the mental image of being in a sexual embrace with him. Terrified, she had run into the kitchen to find her mother. There had been no recurrence of that image until the onset of the current illness, and the incident had remained forgotten until its recall during the interview. Its emergence into consciousness amplified the history of the patient's illness and disclosed an earlier transient outbreak of the same symptoms she had experienced as an adult. After the patient had recovered her composure, she recalled further hitherto forgotten memories. She had slept in her parents' bedroom until she was 6, during which period her father, on one occasion, had taken her into bed and told her stories and, on another, had yelled at her very angrily as she lay in her crib.

During a clinical interview the next day, the patient revealed a fact that she had forgotten in her earlier account of her illness: At the end of the period during which her father had been making the friendly overtures that had so deeply troubled her, and the night before the sudden onset of her symptoms, she had had a nightmare. She was, she dreamed, at a zoo. It was night, and she heard strange noises in the darkness. She asked an attendant standing next to her what the noises were. "Oh," the attendant replied casually, "that's only the animals mating." She then noticed a large, gray elephant lying on its right side in the grass in front of her. As she watched, she noticed the creature moving its left hind leg up and down as if it were trying to get to its feet. At that point she awoke from the dream with a feeling of terror and, afterward, during the morning, experienced the first episode of the frightening imagery of sexual activity with her father.

In direct association to the dream, the patient recalled a long-forgotten childhood memory of an incident that had occurred during her fourth or fifth year. She had awoken one night while in her crib in her parents' bedroom to observe her parents having sexual intercourse. They suddenly became aware of her watching them and sprang apart. The patient remembered seeing her mother hastily pulling up the bedclothes around her to cover her nakedness. Her father, meanwhile, rolled over half on his back, half on his left side. The patient noticed his erection and then saw him lift up his left leg as he sat up and yelled at her angrily to go to sleep.

It was not easy for the patient to communicate these memories. She spoke haltingly, in a low voice and was visibly ashamed and anxious throughout the whole recital of the dream and its associations. She discharged a great quantity of affect, but after doing so, appeared considerably relaxed, relieved, and composed. On her return to the psychiatric ward, she was observed to be cheerful and outgoing with the ward personnel and other patients. Of particular note was that she no longer experienced any anxiety and had no recurrence of the sexual images involving her father that had previously been so deeply distressing. The patient was discharged a short while later after a further series of psychotherapeutic interviews, and when seen for a follow-up visit 2 months later, she reported continued emotional calm and comfort, without recurrence of psychiatric symptoms.



**Table 16.6-2
DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder**

- A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
- B. The person finds it difficult to control the worry.
- C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months).

Note: Only one item is required in children.

 - (1) restlessness or feeling keyed up or on edge
 - (2) being easily fatigued
 - (3) difficulty concentrating or mind going blank
 - (4) irritability
 - (5) muscle tension
 - (6) sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
- D. The focus of the anxiety and worry is not confined to features of an Axis I disorder, e.g., the anxiety or worry is not about having a panic attack (as in panic disorder), being embarrassed in public (as in social phobia), being contaminated (as in obsessive-compulsive disorder), being away from home or close relatives (as in separation anxiety disorder), gaining weight (as in anorexia nervosa), having multiple physical complaints (as in somatization disorder), or having a serious illness (as in hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.
- E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- F. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.

(From American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text rev. Washington, DC: American Psychiatric Association; copyright 2000, with permission.)

circumstance that is the focus of the worry (Table 16.6-2). The distinction between generalized anxiety disorder and normal anxiety is emphasized by the use of the words "excessive" and "difficult to control" in the criteria and by the specification that the symptoms cause significant impairment or distress.

CLINICAL FEATURES

The essential characteristics of generalized anxiety disorder are sustained and excessive anxiety and worry accompanied by a number of physiological symptoms, including motor tension, autonomic hyperactivity, and cognitive vigilance (Table 16.6-3). The anxiety is excessive and interferes with other aspects of a person's life. This pattern must occur more days than not for at least 6 months. The motor tension is most commonly manifested as shakiness, restlessness, and headaches. The autonomic hyperactivity is commonly manifested by shortness of breath, excessive sweating, palpitations, and various gastrointestinal symptoms. The cognitive vigilance is evidenced by irritability and the ease with which patients are startled.



Table 16.6-3
Physiological Symptoms of Anxiety Disorders Explicitly Mentioned in DSM-IV-TR

Panic disorder

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensation of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Chills or hot flushes

Posttraumatic stress disorder

- Physiological reactivity on exposure to trauma-related cues
- Difficulties falling asleep or staying asleep
- Exaggerated startle response

Generalized anxiety disorder

- Muscle tension
- Sleep disturbance

Acute stress disorder

- Marked symptoms of arousal

Patients with generalized anxiety disorder usually seek out a general practitioner or internist for help with a somatic symptom. Alternatively, the patients go to a specialist for a specific symptom (e.g., chronic diarrhea). A specific nonpsychiatric medical disorder is rarely found, and patients vary in their doctor-seeking behavior. Some patients accept a diagnosis of generalized anxiety disorder and the appropriate treatment; others seek additional medical consultations for their problems. Generalized anxiety disorders can be disabling as in the following case.

A 27-year-old married electrician complained of dizziness, sweating palms, heart palpitations, and ringing of the ears of more than 18 months' duration. He also experienced dry mouth and throat, periods of extreme muscle tension, and a constant "edgy" and watchful feeling that had often interfered with his ability to concentrate. These feelings had been present most of the time over the previous 2 years; they had not been limited to discrete periods. Although these symptoms made him feel "discouraged," he denied feeling depressed and continued to enjoy activities with his family.

Because of these symptoms the patient had seen a family practitioner, a neurologist, a neurosurgeon, a chiropractor, and an ear-nose-throat specialist. He had been placed on a hypoglycemic diet, received physiotherapy for a pinched nerve, and been told he might have "an inner ear problem."

He also had many worries. He constantly worried about the health of his parents. His father, in fact, had a myocardial infarction 2 years previously, but is now feeling well. He also worried about whether he is "a good father," whether his wife will ever leave him (there is no indication that she is dissatisfied with the marriage), and whether he is liked by co-workers on the job. Although he recognizes that his worries are often unfounded, he can't stop worrying.

For the past 2 years the patient has had few social contacts because of his nervous symptoms. Although he sometimes had to leave work when the symptoms became intolerable, he continues to work for the same company he joined for his apprenticeship following high-school graduation. He tends to hide his symptoms from his wife and children, to whom he wants to appear "perfect." (Adapted from *DSM-IV-TR Casebook*.)

DIFFERENTIAL DIAGNOSIS

As with other anxiety disorders, generalized anxiety disorder must be differentiated from both medical and psychiatric disorders. Neurological, endocrinological, metabolic, and medication-related disorders similar to those considered in the differential diagnosis of panic disorder must be considered in the differential diagnosis of generalized anxiety disorder. Common co-occurring anxiety disorders also must be considered, including panic disorder, phobias, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD). To meet criteria for generalized anxiety disorder, patients must both exhibit the full syndrome and their symptoms also cannot be explained by the presence of a comorbid anxiety disorder. To diagnose generalized anxiety disorder in the context of other anxiety disorders, it is most important to document anxiety or worry related to circumstances or topics that are either unrelated, or only minimally related, to other disorders. Proper diagnosis involves both definitively establishing the presence of generalized anxiety disorder and properly diagnosing other anxiety disorders. Patients with generalized anxiety disorder frequently develop major depressive disorder. As a result, this condition must also be recognized and distinguished. The key to making a correct diagnosis is documenting anxiety or worry that is unrelated to the depressive disorder.

ONSET AND PROGNOSIS

The age of onset is difficult to specify; most patients with the disorder report that they have been anxious for as long as they can remember. Patients usually come to a clinician's attention in their 20s, although the first contact with a clinician can occur at virtually any age. Only one third of patients who have generalized anxiety disorder seek psychiatric treatment. Many go to general practitioners, internists, cardiologists, pulmonary specialists, or gastroenterologists, seeking treatment for the somatic component of the disorder. Because of the high incidence of comorbid mental disorders in patients with generalized anxiety disorder, the clinical course and prognosis of the disorder are difficult to predict. Nonetheless, some data indicate that life events are associated with the onset of generalized anxiety disorder: The occurrence of several negative life events greatly increases the likelihood that the disorder will develop. By definition, generalized anxiety disorder is a chronic condition that may well be lifelong.

TREATMENT

The most effective treatment of generalized anxiety disorder is probably one that combines psychotherapeutic, pharmacotherapeutic, and supportive approaches. The treatment may take a significant amount of time for the involved clinician, whether the clinician is a psychiatrist, a family practitioner, or another specialist.

Psychotherapy

The major psychotherapeutic approaches to generalized anxiety disorder are cognitive-behavioral, supportive, and insight oriented. Data are still limited on the relative merits of those

approaches, although the most sophisticated studies have examined cognitive-behavioral techniques, which seem to have both short-term and long-term efficacy. Cognitive approaches address patients' hypothesized cognitive distortions directly, and behavioral approaches address somatic symptoms directly. The major techniques used in behavioral approaches are relaxation and biofeedback. Some preliminary data indicate that the combination of cognitive and behavioral approaches is more effective than either technique used alone. Supportive therapy offers patients reassurance and comfort, although its long-term efficacy is doubtful. Insight-oriented psychotherapy focuses on uncovering unconscious conflicts and identifying ego strengths. The efficacy of insight-oriented psychotherapy for generalized anxiety disorder is found in many anecdotal case reports, but large controlled studies are lacking.

Most patients experience a marked lessening of anxiety when given the opportunity to discuss their difficulties with a concerned and sympathetic physician. If clinicians discover external situations that are anxiety provoking, they may be able—alone or with the help of the patients or their families—to change the environment and, thus, reduce the stressful pressures. A reduction in symptoms often allows patients to function effectively in their daily work and relationships and, thus, gain new rewards and gratification that are themselves therapeutic.

In the psychoanalytic perspective, anxiety sometimes signals unconscious turmoil that deserves investigation. The anxiety can be normal, adaptive, maladaptive, too intense, or too mild, depending on the circumstances. Anxiety appears in numerous situations over the course of the life cycle; in many cases, symptom relief is not the most appropriate course of action.

For patients who are psychologically minded and motivated to understand the sources of their anxiety, psychotherapy may be the treatment of choice. Psychodynamic therapy proceeds with the assumption that anxiety can increase with effective treatment. The goal of the dynamic approach may be to increase the patient's anxiety tolerance (a capacity to experience anxiety without having to discharge it), rather than to eliminate anxiety. Empirical research indicates that many patients who have successful psychotherapeutic treatment may continue to experience anxiety after termination of the psychotherapy, but their increased ego mastery allows them to use the anxiety symptoms as a signal to reflect on internal struggles and to expand their insight and understanding. A psychodynamic approach to patients with generalized anxiety disorder involves a search for the patient's underlying fears.

Pharmacotherapy

The decision to prescribe an anxiolytic to patients with generalized anxiety disorder should rarely be made on the first visit. Because of the long-term nature of the disorder, a treatment plan must be carefully thought out. The three major drugs to be considered for the treatment of generalized anxiety disorder are benzodiazepines, the serotonin-specific reuptake inhibitors (SSRIs), buspirone (BuSpar), and venlafaxine (Effexor). Other drugs that may be useful are the tricyclic drugs (e.g., imipramine [Tofranil]), antihistamines, and the β -adrenergic antagonists (e.g., propranolol [Inderal]).

Although drug treatment of generalized anxiety disorder is sometimes seen as a 6- to 12-month treatment, some evidence

indicates that treatment should be long term, perhaps lifelong. About 25 percent of patients relapse in the first month after the discontinuation of therapy, and 60 to 80 percent relapse over the course of the next year. Although some patients become dependent on the benzodiazepines, tolerance rarely develops to the therapeutic effects of the benzodiazepines, buspirone, venlafaxine, or the SSRIs.

Benzodiazepines. Benzodiazepines have been the drugs of choice for generalized anxiety disorder. They can be prescribed on an as-needed basis, so that patients take a rapidly acting benzodiazepine when they feel particularly anxious. The alternative approach is to prescribe benzodiazepines for a limited period, during which psychosocial therapeutic approaches are implemented.

Several problems are associated with the use of benzodiazepines in generalized anxiety disorder. About 25 to 30 percent of all patients fail to respond, and tolerance and dependence can occur. Some patients also experience impaired alertness while taking the drugs and, therefore, are at risk for accidents involving automobiles and machinery.

The clinical decision to initiate treatment with a benzodiazepine should be considered and specific. The patient's diagnosis, the specific target symptoms, and the duration of treatment should all be defined, and the information should be shared with the patient. Treatment for most anxiety conditions lasts for 2 to 6 weeks, followed by 1 or 2 weeks of tapering drug use before it is discontinued. The most common clinical mistake with benzodiazepine treatment is routinely to continue treatment indefinitely.

For the treatment of anxiety, it is usual to begin giving a drug at the low end of its therapeutic range and to increase the dosage to achieve a therapeutic response. The use of a benzodiazepine with an intermediate half-life (8 to 15 hours) will likely avoid some of the adverse effects associated with the use of benzodiazepines with long half-lives, and the use of divided doses prevents the development of adverse effects associated with high peak plasma levels. The improvement produced by benzodiazepines may go beyond a simple antianxiety effect. For example, the drugs may cause patients to regard various occurrences in a positive light. The drugs can also have a mild disinhibiting action, similar to that observed after ingesting modest amounts of alcohol.

Buspirone. Buspirone is a 5-HT_{1A} receptor partial agonist and is most likely effective in 60 to 80 percent of patients with generalized anxiety disorder. Data indicate that buspirone is more effective in reducing the cognitive symptoms of generalized anxiety disorder than in reducing the somatic symptoms. Evidence also indicates that patients who have previously had treatment with benzodiazepines are not likely to respond to treatment with buspirone. The lack of response may be caused by the absence, with buspirone treatment, of some of the nonanxiolytic effects of benzodiazepines (e.g., muscle relaxation and the additional sense of well-being). The major disadvantage of buspirone is that its effects take 2 to 3 weeks to become evident, in contrast to the almost immediate anxiolytic effects of the benzodiazepines. One approach is to initiate benzodiazepine and buspirone use simultaneously, then taper off the benzodiazepine use after 2 to 3 weeks, at which point the buspirone should have reached its maximal effects. Some studies have

also reported that long-term combined treatment with benzodiazepine and buspirone may be more effective than either drug alone. Buspirone is not an effective treatment for benzodiazepine withdrawal.

Venlafaxine. Venlafaxine is effective in treating the insomnia, poor concentration, restlessness, irritability, and excessive muscle tension associated with generalized anxiety disorder. Venlafaxine is a nonselective inhibitor of the reuptake of three biogenic amines—serotonin, norepinephrine, and, to a lesser extent, dopamine.

Selective Serotonin Reuptake Inhibitors. SSRIs may be effective, especially for patients with comorbid depression. The prominent disadvantage of SSRIs, especially fluoxetine (Prozac), is that they can transiently increase anxiety and cause agitated states. For this reason, the SSRIs sertraline (Zoloft), citalopram (Celexa), or paroxetine (Paxil) are better choices in patients with high anxiety disorder. It is reasonable to begin treatment with sertraline, citalopram, or paroxetine plus a benzodiazepine, then to taper benzodiazepine use after 2 to 3 weeks. Further studies are needed to determine whether SSRIs are as effective for generalized anxiety disorder as they are for panic disorder and OCD.

Other Drugs. If conventional pharmacological treatment (e.g., with buspirone or a benzodiazepine) is ineffective or not completely effective, then a clinical reassessment is indicated to rule out comorbid conditions, such as depression, or to better understand the patient's environmental stresses. Other drugs that have proved useful for generalized anxiety disorder include the tricyclic and tetracyclic drugs. The β -adrenergic receptor antagonists may reduce the somatic manifestations of anxiety, but not the underlying condition, and their use is usually limited to situational anxieties, such as performance anxiety.

REFERENCES

- Ball SG, Kuhn A, Wall D, Shekhar A, Goddard AW. Selective serotonin reuptake inhibitor treatment for generalized anxiety disorder: A double-blind, prospective comparison between paroxetine and sertraline. *J Clin Psychiatry*. 2005;66(1):94-99.
- Brawman-Mintzer O, Monnier J, Wolitzky KB, Falssetti SA. Patients with generalized anxiety disorder and a history of trauma: Somatic symptom endorsement. *Journal of Psychiatric Practice*. 2005;11(3):212-215.
- Ginsberg DL, ed. Women and anxiety disorders: Implications for diagnosis and treatment. *CNS Spectrums*. 2004;9:1-16.
- Heimberg RG, Turk CL, McNamara DS, eds. *Generalized Anxiety Disorder: Advances in Research and Practice*. New York: Guilford Press; 2004.
- Le Roux H, Gatz M, Wetherell JL. Age at onset of generalized anxiety disorder in older adults. *Am J Geriatr Psychiatry*. 2005;13:23-30.
- Rickels K, Rynn M, Iyengar M, Duff D. Remission of generalized anxiety disorder: A review of the paroxetine clinical trials database. *J Clin Psychiatry*. 2006;67(1):41-47.
- Rodriguez BF, Bruce SE, Pagano ME, Keller MB. Relationships among psychosocial functioning, diagnostic comorbidity, and the recurrence of generalized anxiety disorder, panic disorder, and major depression. *J Anxiety Disord*. 2005;19(7):752-766.
- Rollman BL, Belnap BH, Mazumdar S, Zhu F, Kroenke K, Schulberg HC, Shear MK. Symptomtic severity on Prime-MD diagnosed episodes of panic and generalized anxiety disorder in primary care. *J Gen Intern Med*. 2005;20:623-628.
- Shear K, Belnap BH, Mazumdar S, Houck P, Rollman BL. Generalized anxiety disorder severity scale (GADSS): A preliminary validation study. *Depress Anxiety*. 2006;23(2):77-82.
- Steffens DC, McQuoid DR. Impact of symptoms of generalized anxiety disorder on the course of late-life depression. *Am J Geriatr Psychiatry*. 2005;13:40-47.

▲ 16.7 Other Anxiety Disorders

ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION

Many medical disorders are associated with anxiety. Symptoms can include panic attacks, generalized anxiety, obsessions and compulsions, and other signs of distress. In all cases, the signs and symptoms will be due to the direct physiological effects of the medical condition.

Epidemiology

The occurrence of anxiety symptoms related to general medical conditions is common, although the incidence of the disorder varies for each specific general medical condition.

Etiology

A wide range of medical conditions can cause symptoms similar to those of anxiety disorders (Table 16.7-1). Hyperthyroidism (see Color Plate 16.7-1 on page 494), hypothyroidism, hypoparathyroidism, and vitamin B₁₂ deficiency are frequently associated with anxiety symptoms. A pheochromocytoma produces epinephrine, which can cause paroxysmal episodes of anxiety symptoms. Certain lesions of the brain and postencephalic states reportedly produce symptoms identical to those seen in obsessive-compulsive disorder (OCD). Other medical conditions, such as cardiac arrhythmia, can produce physiological symptoms of panic disorder. Hypoglycemia can also mimic the symptoms of an anxiety disorder. The diverse medical conditions that can cause symptoms of anxiety disorder may do so through a common mechanism, the noradrenergic system, although the effects on the serotonergic system are also under study. Each of these conditions is characterized by prominent anxiety that arises as the direct result of some underlying physiological perturbation.

Diagnosis

The text revision of the fourth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) diagnosis of anxiety disorder due to a general medical condition (Table 16.7-2) requires the presence of symptoms of an anxiety disorder. DSM-IV-TR allows clinicians to specify whether the disorder is characterized by symptoms of generalized anxiety, panic attacks, or obsessive-compulsive symptoms.

Clinicians should have an increased level of suspicion for the diagnosis when chronic or paroxysmal anxiety is associated with a physical disease known to cause such symptoms in some patients. Paroxysmal bouts of hypertension in an anxious patient may indicate that a workup for a pheochromocytoma is appropriate. A general medical workup may reveal diabetes, an adrenal tumor, thyroid disease, or a neurological condition. For example, some patients with complex partial epilepsy have extreme